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Nano-engineered electro-responsive drug delivery systems

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Abstract

Stimuli-responsive drug delivery systems can release therapeutic agents when actuated by an appropriate stimulus, whether endogenous or exogenous. Interestingly, exogenous stimuli are completely dissociated from the patient's physiology and can be precisely controlled externally in magnitude, in space, and in time. They can therefore constitute more reproducible means of controlling the release of therapeutics from appropriately responsive delivery systems. One stimulus which has long attracted attention is the application of an electric potential, and most electro-responsive drug delivery systems reported to date have been based on intrinsically conducting polymers. These systems, however, are limited by slow drug release and low drug loading. These challenges are currently driving the development of new electro-responsive delivery systems with higher responsiveness and drug loading, by implementing concepts of nano-engineering into their structure. This review will focus on this exciting and most recent direction taken in the field by first discussing drug delivery from electro-responsive films containing nano-scaled features, and then nanoscale dispersed/colloidal electro-responsive drug delivery systems, such as nanoparticles, micelles, and vesicular structures.

Keywords

Electro-responsive; Films; Ultrathin; Nano-structured; Nano-porous; Switches; Composites; Nanoparticles; Micelles; Vesicles

1. Introduction

Stimuli-responsive drug delivery systems can release therapeutic agents by actuation from endogenous factors such as temperature, pH, redox potential, or the presence reactive biomolecules (*e.g.*, enzymes).[1-5] Such systems continue to receive considerable interest from the community, though one major challenge lies in how pronounced the endogenous stimulus manifests itself in diseased versus healthy tissue. When the difference is small, specifically targeting diseased tissue can be challenging due to off-target release. In addition, patient-to-patient variability can affect the reproducibility of release. In contrast, exogenous factors are completely dissociated from the patient's physiology and can be precisely controlled externally in magnitude, in space, and in time. They could therefore constitute more reproducible means of controlling the release of therapeutics from appropriately responsive systems. Several exogenous stimuli have been explored for this purpose, including magnetic fields, light, heat, ultrasounds, *etc*.[4, 6-8] An additional stimulus that has long attracted attention is the application of an electric potential.[4, 9-12] This is mainly due to the low cost, simplicity, and portability of the control equipment, which make it amenable for personalized or even "pharmacy-on-a-chip" applications.[13] Furthermore, the ability to implant (micro)electrodes in the body implies that delivery systems can be envisaged for applications anywhere, for example in areas that can be inaccessible to conventional drug delivery systems (*e.g.*, in the brain), or where it is impractical to use other endogenous/exogenous stimuli.

Electro-responsiveness can be achieved using molecules that spontaneously orient their dipoles with applied electric fields. However, responsiveness is more commonly obtained using molecules that undergo an electrically-induced redox reaction. Indeed, most electro-responsive drug delivery systems reported to date are based on intrinsically conducting polymers (ICPs), such as poly(pyrrole) (PPy).[11, 12] Early work in this area has involved implantable bulk ICP materials and hydrogels for the sustained or on-demand release of therapeutics.[10-12, 14-17] ICPs, in their oxidized form, possess multiple positive charges along their backbone that can serve as sites for complexing negatively-charged drugs (dopant molecules). Drug release is triggered from these systems by reduction of the ICP, which becomes neutral and thereby expels the drug out of the ICP matrix towards the external medium. One important limitation of this technology is that mass transport in bulk ICPs is slow, which renders the corresponding release process slow. Another important challenge is that the range of drugs amenable to this technology is restricted by the charge/size requirements of dopant molecules, and that bulk ICPs have limited capacity for drug loading. These challenges are currently driving the development of new electro-responsive delivery systems, many of which remain based on ICPs, with higher responsiveness/drug loading, and with less drug release in the absence of an electric field. In addition, the development of systems able to release drugs other than small anionic molecules is highly desirable.

To address these challenges, the concept of nano-engineering the structure of electro-responsive drug delivery systems has been investigated. Indeed, in many other fields, nano-engineering has made a pronounced impact because nanoscale features lead to high surface-to-volume ratios,[1, 4, 18-21] which accelerates processes involving exchange with the external

environment. In addition, nano-sized reservoirs can act as depots for increasing drug loading, without compromising responsiveness. This review will focus on this exciting and most recent direction taken in the field of nano-electro-responsive drug delivery systems. Bulk electro-responsive materials and hydrogels are not discussed, nor is the application of high trans-membrane voltage for the transient formation of pores in cell membranes (*i.e.*, iontophoresis), to increase their permeability.[22] In addition, drug release must be directly triggered by an electric stimulus, and not indirectly such as by a change of local pH caused by the electro-oxidation/reduction of water (or dissolved oxygen),[23] or by chemical oxidants or reducing agents.[5, 24-26] This contribution first discusses drug delivery from electro-responsive films containing nano-scaled features and is followed by a presentation of nanoscale dispersed/colloidal electro-responsive drug delivery systems (nanoparticles, micelles, and vesicular structures).

2. Electro-responsive films

Considering that PPy can be conveniently electro-polymerized in a controlled manner directly on the surface of any conductive substrate, it is not surprising that most reports involving ICPs have involved thin films on electrodes. Charged drugs can be directly incorporated into the growing film during the electro-polymerization process, or can be loaded afterwards. Such films have, for example, been used as coatings for neural prostheses to release anti-inflammatory agents, or to promote neural growth.[27, 28] *In vivo*, these systems were shown to promote slight increase of neural density without affecting fibrous tissue formation.[29] Furthermore, the polymer-coated electrodes possessed similar impedance to platinum electrodes, implying that the coating does not detract from the original purpose of the implant, which is to deliver electric current to neurons. In general, while control of drug release by manipulation of the electric stimulation was possible, increasing responsiveness (e.g., from days to hours or minutes) and/or drug loading would be advantageous. This section discusses means to accomplish this, such as by preparing nano-textured films, creating ultra-thin films, templating films on nano-structured substrates, introducing nano-porosity, using films as switches for nano-porous drug reservoirs, and adding nanomaterials as functional fillers within nano-composites.

2.1 Nano-textured films

Electro-polymerized PPy films prepared on flat electrodes typically display caulilower-like morphologies (**Figure 1a**).[30] Due to the low surface area of this morphology, the rate of release of doped payloads can be slow. However, it has been observed that the dopant molecule itself can direct the morphology of the prepared film. For instance, adenosine triphosphate (ATP), used as dopant and model drug, produced a nano-wire PPy network morphology (**Figure 1b**) with a substantially higher surface area than the corresponding cauliflower morphology. Upon application of a reducing potential (–0.8 V vs. saturated calomel electrode (SCE)), 53 % of ATP was released from the cauliflower-like PPy film in 48 h (most of which during 24 h), while 90 %

of ATP was released for PPy nanowires in the same time. Furthermore, when large amounts of nanowires are produced, they can form a network whose cavities can act as depots for additional drugs. That is, by covering the porous network with an additional capping electro-active film, the drug can be entrapped into the cavities, which then act as drug reservoirs (see Section 2.5).[31] It is also interesting to note that a nano-tentacle morphology was obtained for PPy films produced on gold electrodes using sodium *p*-toluene sulfonate as doping agent (**Figure 1c**).[32] A better understanding of the morphology-directing effect of dopants would be interesting to harness this strategy for the rational design of future nano-structured films.

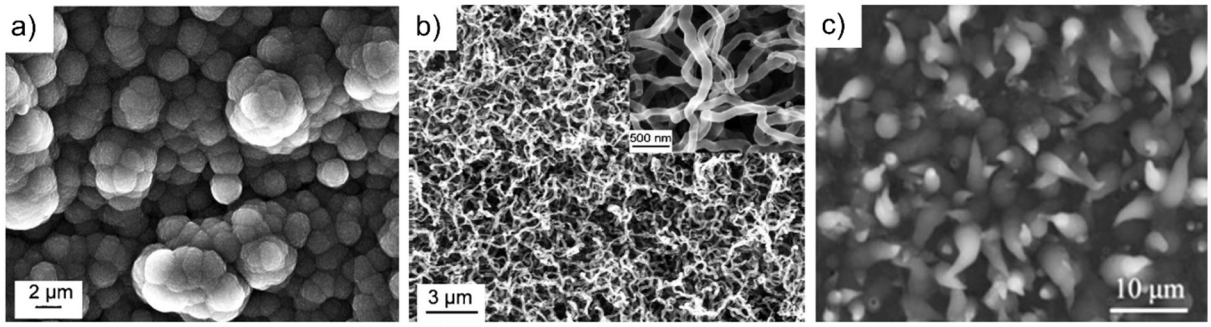

Figure 1| **Dopants can direct the morphology of electro-polymerized PPy films**. Scanning electron micrographs of PPy films displaying (a) cauliflower morphology, (b) nano-wire morphology due to the use of ATP as dopant, and (c) nano-tentacle morphology due to the use of sodium *p*-toluenesulfonate as dopant. Adapted with permission from Refs.[30, 32]

2.2 Ultrathin films on bulk substrates

Ultrathin layered polyelectrolyte films, which can be prepared by the so-called layer-by-layer (LbL) technique, can be used to encapsulate and ultimately release therapeutic agents.[33-35] Assembly of the films generally involves the sequential and repetitive electrostatic complexation of charged (macro)molecules onto an oppositely-charged layer, bound to a substrate. Song *et al.*[36] have prepared a multilayer electro-responsive film by LbL assembly of organometallic poly(ferrocenylsilanes) (PFS; **Figure 2a**). Iron within the PFS backbone can be reversibly switched between ferrocene and ferrocenium, and this process serves as a transducer of redox signals. Two PFS analogs, one bearing positively charged side-chains and the other negatively charged ones, were used to build up the multilayer (PFS^+ and PFS^-, respectively, in **Figure 2a**). Alexa 488-labeled dextran was used as basic molecule for observation of release, and tetramethylrhodamine-labeled dextran was employed as a second release guest. These were incorporated at different locations within the multilayers. Dissassembly of the electro-responsive film was electrochemically-controlled by prolonged exposure to a low oxidation potential (+0.6 V vs. Pt). This induced charge imbalance and an electrostatic repulsion force between the charged polyelectrolyte domains, together with osmotic pressure, contributed to multilayer disassembly.

By assembling these redox active multilayers on top of redox-inactive ones (~9 nm thick; five bilayers), the authors slowed the rate of release from the electro-responsive film to a rate comparable to that observed without the oxidizing potential. Using the LbL method, complex film structures can be prepared, and the drug-containing layers can be positionned as desired (**Figure 2a**). Recksiedler *et al.*[37] have prepared a conducting multilayer film by LbL assembly of poly(aniline boronic acid) and ribonucleic acid. The polymers can interact through the formation of boronate esters, a boron–nitrogen dative bond, and electrostatic interactions (**Figure 2b**). The authors have demonstrated release of the ribonucleic acid by cycling the potential applied to the multilayer between –0.2 and +1.4 V (vs. Ag/AgCl). Thin films prepared by electro-polymerization can also be used as functional coatings for bulk materials, other than flat electrodes. For instance, Esrafizadeh *et al.*[38] have prepared a conducting core fiber of poly(3,4-ethylenedioxythiophone) (PEDOT):poly(styrene sulfonate), which they use as a scaffold for neural tissue engineering. This conducting scaffold was then coated with a thin PPy film containing the antibiotic ciprofloxacin hydrochloride, as dopant. The conductivity of the overall structure also provided an electric contact between the drug releasing film and neural cells.

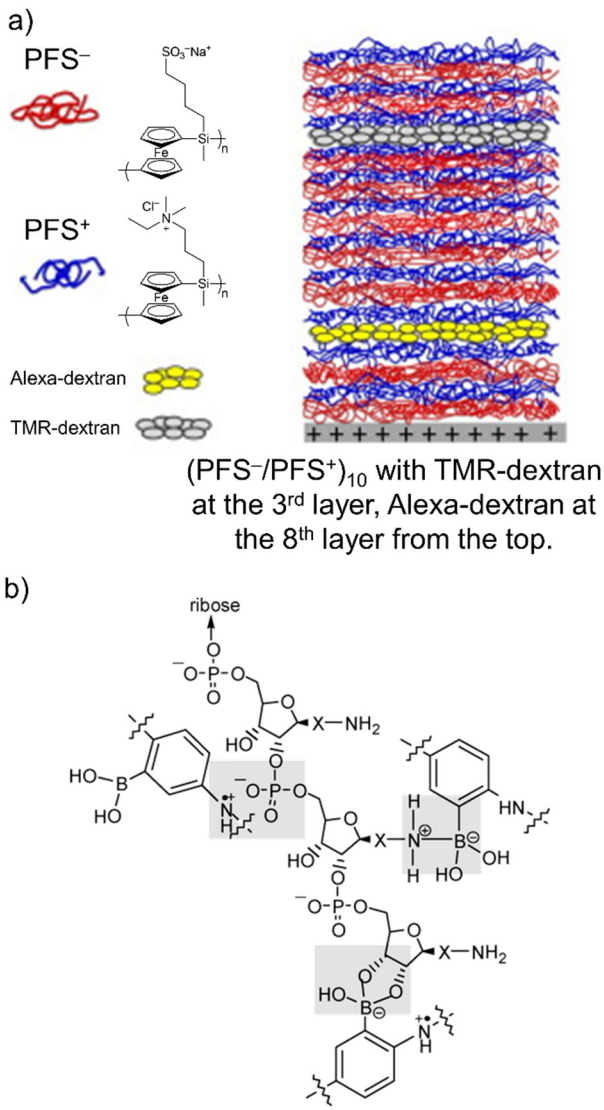

Figure 2| **Electro-responsive ultrathin films**. (a) Polyelectrolyte multi-layers prepared with electro-responsive PFS building blocks release complexed model therapeutic agents, such as Alexa 488-labelled dextran (Alexa-dextran) or tetramethylrhodamine-labeled dextran (TMR-dextran). These can be placed at any location within the multi-layer. (b) Proposed poly(aniline boronic acid)–ribonucleic acid bilayer interactions: boronate−ester formation, boron−nitrogen dative bond formation, and/or electrostatic interactions. Adapted with permission from Refs.[36, 37]

2.3 Films on nano-featured substrates

The fabrication of films on substrates displaying nano- or micro-scaled features has also been investigated as a means for increasing their electro-responsiveness. For instance, the encapsulation of drugs into biodegradable polymer nano-fibers can be achieved by electrospinning.[39, 40] Then, an ICP sheath can be added on the pre-spun nanofibers. This strategy has been used to prepare neural prostheses, with the ICP enabling electric contact with neurons.[38, 41, 42] Alternatively, Leprince *et*

al.[43] have electro-polymerized a PPy film incorporating the anti-inflammatory drug dexamethasone (DEX) onto a platinum electrode structured with an array of metallic nanopillars (**Figure 3a**). This array was obtained by electro-deposition of the metal within the nanopores of a sacrificial gold-coated polycarbonate template. The nanopillar array was reported to improve adherence between the film and the electrode as well as increase the electro-activity of the PPy film. Of course, as for films on planar substrates, electro-activity was reported to be progressively lost, partly through loss of dopant molecules and through possible over-oxidation of the film (**Figure 3a**). Using a similar rationale, Thompson *et al.*[44] aligned carbon nano-tubes perpendicular to the surface of a platinum electrode. A PPy layer doped with neurotrophin-3 was coated onto their surface by electro-polymerization, yielding a nano-textured film. Due to the high surface area of the film, efficient release of NT-3 from the nanostructured electrode was achieved upon electrical stimulus. A ten-fold increase of release rate was observed compared to a film on a flat substrate (**Figure 3b**).

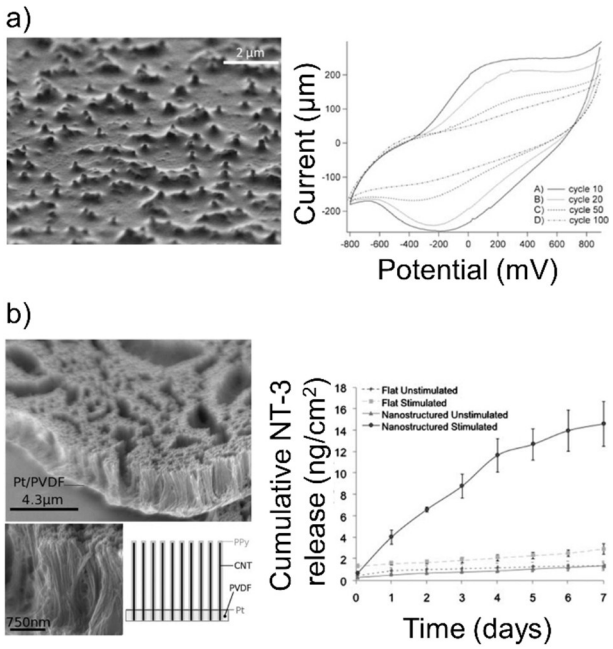

Figure 3| **Drug release from thin films on nano-structured substrates**. (a) A thin film of PPy on an array of platinum nanopillars. Expected progressive loss of electro-activity with cycling. (b) Thin PPy films on arrays of carbon nano-tubes release entrapped neurotrophin-3 (NT-3) at a significantly greater rate than from non-nano-structured films. Adapted with permission from Refs.[43, 44]

2.4 Nano-porous films

Architecturally-complex nano-porous ICP films can be conveniently prepared by colloidal lithography.[45] In this technique, polymer nanoparticles are used as templates for nano-pores, and

are packed onto an electrode. The electrode is then immersed into a monomer solution (containing the drug), which is then electro-polymerized in the interstitial spaces of the assembled nanoparticles. Removing the sacrificial nanoparticles by dissolution in an appropriate solvent reveals the porous structure of the film. In an elegant example of the structures that can be created using this method, Pokki *et al.*[46] have prepared a nano-porous PPy film incorporating rhodamine B, used as model drug, and have examined its passive release into the medium (**Figure 4a**). Unfortunately, electro-responsive drug release was not examined. Luo and Cui have prepared a nano-porous PPy film on a glassy carbon electrode using poly(styrene) nanoparticles as templates.[47] Fluorescein, which was used as a model drug, could be released upon exposure to a negative potential. In comparison to a non-porous film (*i.e.*, prepared without the colloidal template), the rate of release was significantly faster (~9 times faster at –2 V vs. Ag/AgCl), with most of the drug being released within ~1 minute (**Figure 4b**). These results were explained by efficient mass transport towards the external medium, due to the high surface-to-volume ratio of the film. Moreover, passive diffusion of the fluorescein from the nano-porous PPy film was negligible (3% of the drug electro-chemically released), indicating that it is a true command-driven release system. The amount of drug released increased gradually with the increase of the cathodic potential value. Rather than entrapping and releasing small drugs, Cho and Borgens have prepared a nano-porous PPy film doped with biotin,[48] which served to anchor 5 nm streptavidin-coated gold nanoparticles (exploiting biotin–streptavidin interaction). When the surfaces were subjected to a negative electric potential, the system was able to release a higher amount streptavidin–gold nanoparticles than in the absence of such a field. This strategy could be of interest for the delivery of other types of nanoparticles, including therapeutic ones. Sharma *et al.*[49] have prepared a nano-porous PPy film into which they encapsulate the anti-psychotic drug risperidone. In a final step, the film was capped by electro-polymerization of a non-porous PPy overlayer, devoid of drug. Compared to the nano-porous films above, drug release upon exposure to an electric potential was substantially slower (in the range of an hour or so) because the drug must diffuse through the capping layer, whose thickness can be controlled. This approach could be interesting to have drug release over a longer period of time. Upon application of an alternating pulsed potential (±0.6 V vs. Ag/AgCl; 0.5 Hz), the films rapidly cycled between reduced and oxidized states which caused them to alternatively expand and contract. This change in volume was associated with hydrated ions moving in and out of the polymer, and correlated to increased rates of drug release.

Another way of introducing porosity into films is to prepare films from nanocapsules. Crespy and co-workers[50, 51] have developed controlled-release electro-responsive ICP nano-capsules for the development of self-healing corrosion-protection coatings for metals (**Figure 4c**). This concept could be extended for controlled release of therapeutics. Charged 3-nitrosalicylic acid (anti-corrosion agent) was encapsulated into the nano-capsules by mini-emulsion polymerization. The nano-capsules could be decorated with gold nanoparticles, to ensure a stable electronic contact with the underlying metal to protect (*i.e.*, to circumvent the possibility of a Fermi-level misalignment). Fast release of 3-nitrosalicylic acid from poly(aniline) nano-capsules was detected by UV–vis spectroscopy upon a reductive trigger at –0.5 V (vs. SHE). During the

reduction process, potassium cations were introduced into the nano-capsule membrane. Thus, the nano-capsules expanded and the permeability of the membrane increased. However, release was hindered by an oxidative trigger. For instance, at +0.5 V (vs. SHE), the shell became more compact and thus the permeability of the shell decreased. Similar observations were made for the hydrophobic anti-corrosion agents, though these films appeared to release more anti-corrosive agent in the absence of electric potential than when charged agents were investigated.

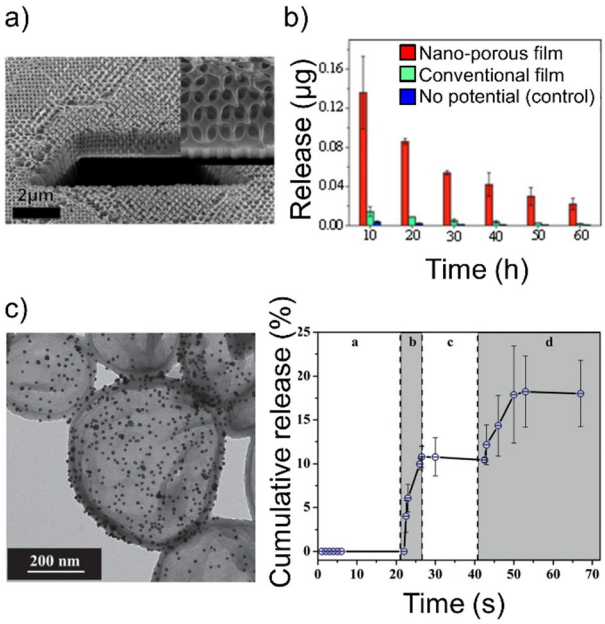

Figure 4| **Drug delivery from electro-responsive nano-porous films**. (a) Scanning electron microscopy image of an exemplary nano-porous film prepared by colloidal lithography. (b) Release of fluorescein upon exposure to an electric potential is substantially faster from a nano-porous film than from a conventional one, or in the absence of potential. (c) Gold nanoparticle-decorated ICP nano-capsules are used to prepare coatings for metals. Release of entrapped substances is very fast upon exposure to a reducing potential (areas "b" and "d" in graph). Adapted with permission from Refs. [46, 47, 50]

2.5 Switches on the surface of nano-porous materials

ICP films can be used as nano-switches to gate the release of therapeutics from other materials, which do not necessarily need to be electro-responsive. For instance, the cavities in nano-porous films can act as depots for payloads that can be sealed with a thin ICP film. Application of an electric potential actuates the contraction/expansion of the ICP, which changes the permeability of the capping film. Luo and Cui have created a nano-porous PPy film by colloidal lithography and have loaded two different payloads.[52] The first payload, fluorescein, was doped within the PPy matrix during electro-polymerization, and the anti-inflammatory agent DEX was

loaded into the nano-pores. Both payloads were released upon exposure to negative potentials. This strategy can be used to physically encapsulate additional drugs that do not comply with the requirements of being dopants within PPy. A related example was reported by Jiang *et al.*,[31] who have created a porous PPy network of nanowires, which they cap with a PPy film by chemical vapor deposition. The porous network could be loaded with both hydrophilic and lipophilic drugs, owing to the amphiphilicity of the PPy nanowire network. The authors stimulated drug release by cycling between –0.9 to +0.6 V (vs. SCE) in a repetitive manner and observed a greater release at higher scanning rates (*i.e.*, 200 $mV \cdot s^{-1}$ versus 50 $mV \cdot s^{-1}$), which they attributed to the larger number of contraction and expansion cycles the film undergoes over the 10-h period examined.

Jeon *et al.*[53] have covered a nano-porous anodized aluminum oxide membrane with a thin PPy layer (**Figure 5a**). To accomplish this, the top and the side walls of the membrane were first covered with a thin layer of gold. Then, PPy doped with dodecylbenzenesulfonate was electro-polymerized on the gold layer. Nano-porous anodized aluminum oxide membranes are available commercially with regular pore sizes and high pore density. They have found different applications in photonic devices, magnetic storage, and biotechnology.[54-56] The thickness of the PPy layer was very small (~1.5 μm) compared to the overall thickness of the membrane (60 μm), due to the limited penetration of gold into the pores during the metallization step. To control pore size with an electrical stimulus, the membrane was oxidized at +0.1 V and reduced at −1.1 V (vs. Ag/AgCl). The electro-induced volume change of PPy was the driving force for opening/shutting the pores. PPy chains shrank in the oxidation state due to the expulsion of hydrated sodium ions.[57] Oppositely, PPy chains expanded to cover the pores in the reduced state. Atomic force microscopy images confirmed the reversible changes of pore sizes, which correlated to the flux of an electrolyte through the membrane (**Figure 5b**). To further analyze the open vs. closed status of the pores, permeation of fluorescein-labeled bovine serum albumin through the membrane was evaluated. ON/OFF type release of the protein was achieved by appropriate switching of stimulus (**Figure 5c**). The PPy-coated membrane responded to electrical stimuli within a few seconds and was very stable, even after 1000 repeated redox cycles. From a fabrication point of view, Abelow *et al.*[58] have described the vapor phase synthesis of PPy and PEDOT doped with iron(III) chloride and *p*-toluenesulfonate on aluminum oxide nano-porous membranes. Such a preparation method is considerably more flexible compared to electro-polymerization, since an electrically-conductive substrate is not a requirement for successful polymerization.

ICP films can also be used to control and potentially switch ON/OFF the the dissolution of a bulk material. For instance, Abidian *et al.*[59] have electrospun nano-fibers of biodegradable polyesters containing DEX onto a micro-fabricated electrode. The nanofibers were then covered with a PEDOT film doped with phosphate-buffered saline, which prevented undesired drug release, caused by erosion of the polyester in contact with the external aqueous environment. Without the protective PEDOT layer, 75% of DEX was released from the nanofibers in one week. However, less than 25% of DEX was released after 54 days when covered with the PEDOT layer. The release of DEX was also achieved in a pulsatile fashion by using electrical potential. Indeed, upon application of +1.0 V vs Ag/AgCl, abrupt release of DEX was detected in the external medium,

possibly due to cracks in the coating generated during contraction. A related system has also been evaluated in neural microelectrode arrays.[60]

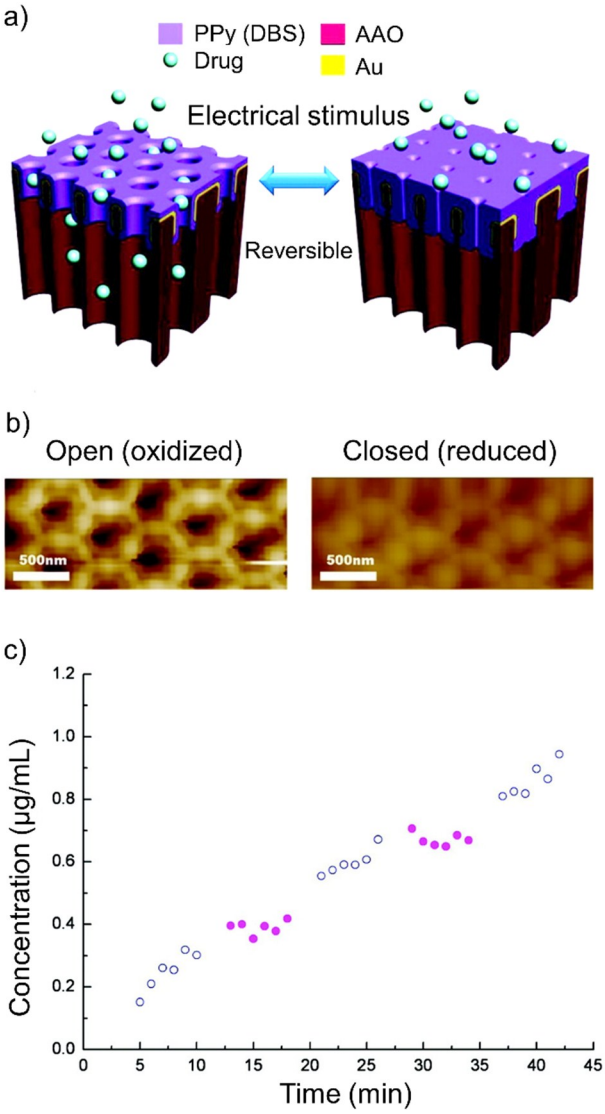

Figure 5| **Drug delivery exploiting electro-responsive gates for drug reservoirs.** (a) Anodized aluminum oxide (AAO) membrane covered with gold onto which is electro-polymerized PPy doped with sodium dodecylbenzenesulfonate; (b) Reversible change of pore size can be evidenced by atomic force microscopy. (c) The cumulative concentration of fluorescent bovine serum albumin with time from a membrane with initial pore diameter of 110 nm. Open (blue) and closed (magenta) circles represent the oxidized and reduced states of the PPy film. Adapted with permission from Jeon *et al.*[53]

2.6 Nano-composite films

Functional filler materials introduce an additional parameter with which to manipulate the properties of electro-responsive films. For instance, Xiao *et al.*[61] have prepared an electro-responsive film composed PEDOT doped with DEX and containing single-wall carbon nano-tubes (SWNT). The presence of SWNTs greatly improved conductivity of the film and, in combination to the composite exhibiting a petal-like surface morphology (20–30 nm thick and 100–200 nm wide), imparted a higher rate of drug release compared to pure PEDOT. Alternaltively, Luo *et al.*[62] have exploited multi-wall carbon nano-tubes (MWCNTs) as nano-reservoirs for loading drugs into an ICP film. Acid treatment combined with sonication opened the MWCNT ends, and made their inner and outer surfaces more hydrophilic. Thus, when dispersed in an aqueous solution of DEX, they fill with drug. To prevent unwanted release, the MWCNTs were incorporated into a film of PPy, which sealed their ends. Two different square wave potentials were used for drug release: Aggressive stimulation, used for rapid drug release, was achieved by applying –2 V (vs. Ag/AgCl) for 5 s, then 0 V for 5 s in a repetitive manner. Alternatively, the authors applied –0.5 V for 5 s followed by +0.5 V for 5 s for mild stimulation and to achieve sustained drug release. A two-fold increase in drug loading was achieved by incorporation of MWCNT nano-reservoirs. In order to fabricate an electro-responsive LbL film, Sun *et al.*[63] have prepared positively charged electro-responsive micelles composed of poly(ethylene imine) (PEI) bearing a ferrocene end-group. Self-assembly sequestered the hydrophobic ferrocene units (when in their reduced state) into the core of the micelle, and were used as cationic entities for LbL film assembly alongside negatively-charged DNA (**Figure 6a**). The authors encapsulsated the model hydrophobic drug pyrene, and observed that repetitive application of an oxidizing potential of +0.5 V (vs. Ag/AgCl) produced stepwise and reproducible release of the drug. Oxidation of ferrocene produced a positive charge, which was rationalized to trigger a hydrophobic to hydrophlic transition of the core of the micelles. DNA, which remained electrostatically complexed to PEI, remained intact, and only a small amount of drug release was observed when the potential was removed. The use of small oxidizing potentials could be beneficial because of lesser undesired side-reactions. In another interesting example, Wood *et al.*[64] have constructed mutilayer films composed of PEI and Prussian Blue. Prussian Blue can be synthesized in the form of polydisperse, anionic nanoparticles (median size 4–5 nm) that are stable in aqueous solution and can be used as the anionic component of LbL films. ^{14}C-dextran sulfate (^{14}C-DS), used as model drug, was used as a second negatively-charged component. It was incorporated every second negative layer to produce a tetra-layer type system (each tetra-layer being ~4.2 nm thick), rather than a conventional bilayer system. Upon application of an oxidizing potential of +1.25 V (vs. SCE), the negatively-charged Prussian Blue was oxidized to its neutral Prussian Brown form, resulting in rapid destabilization of the film and release of its components within 10 min. As expected, the release of ^{14}C-DS from the film was faster with electrical stimulus than without, and a decrease in film thickness was observed over time. More interestingly, the release of ^{14}C-DS displayed ON/OFF behavior with the electric field (**Figure 6b**). More recently, the same group reported the LbL assembly of Prussian Blue nanoparticles and gentamicin, a small positively-charged antibiotic.[65] Films with thicknesses in the range of 100–500 nm were prepared, yielding drug loadings of ~1–4 $\mu g \cdot cm^{-2}$. Release was dependant on film

thickness and the magnitude of the applied oxidizing potential. Atomic force microscopy revealed that the electrochemically-dissolved films did not change their surface roughness (or a small decrease). This observation suggested that the films dissolved by surface erosion. In the absence of applied potential, 10–15 % of the small drug was released from the film over 1 h, which the authors suggested to be due to the inherent instability of Prussian Blue at alkaline pH. The authors therefore proposed that such a system could be of interest for specific shorter-term medical applications and/or different methods should be sought out to enhance the pH-stability of the films.

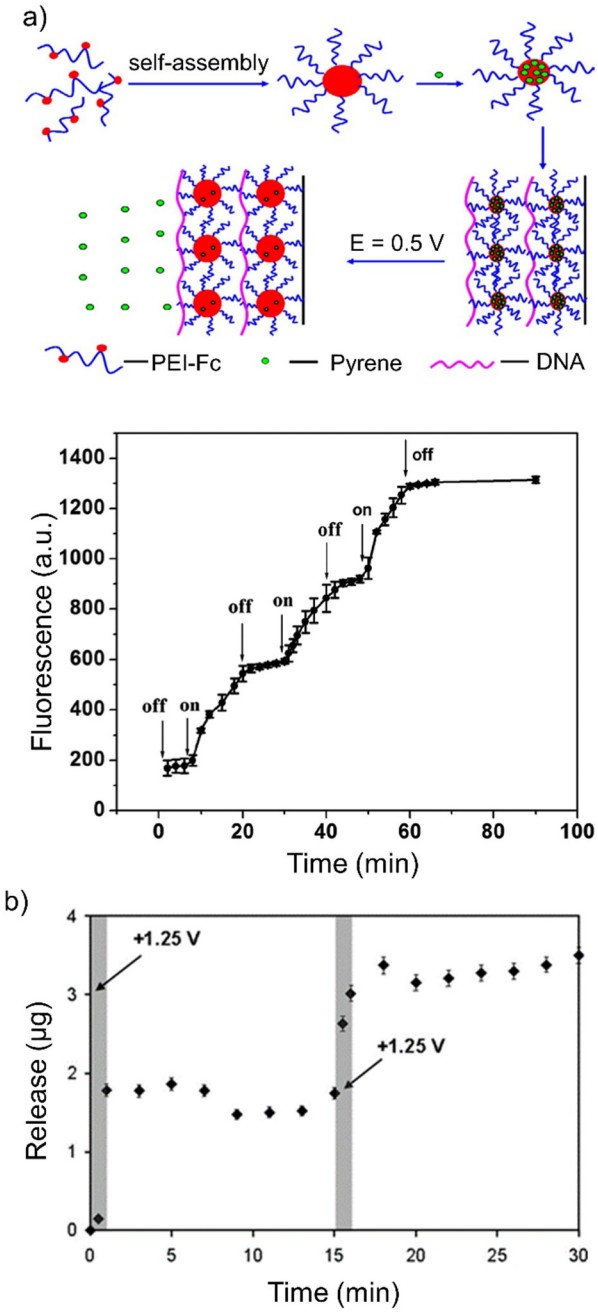

Figure 6| **Drug release from electro-responsive nano-composite films**. (a) Illustration of the LbL assembly deoxyribonucleic acid and micelles of poly(ethylene imine) (PEI) bearing a ferrocene (Fc) end-group. Controlled ON/OFF release of pyrene from within the micelles by applying an electric potential. (b) ON/OFF switchable destabilization of Prussian Blue-containing (PEI/Prussian Blue/PEI/^{14}C-dextran sulfate)$_{30}$ films. Release of ^{14}C-dextran sulfate at +1.25 V for 1-min intervals at t = 0 and 15 min. Adapted with permission from Refs. [63, 64]

3. Dispersed electro-responsive delivery systems

In addition to films, electro-responsive drug delivery systems can also be designed as dispersible or colloidal entities. Indeed, colloidal drug delivery systems have been extensively examined for their ability to encapsulate drugs and release them upon exposure to a variety of triggers, such as local pH, temperature, and light.[6, 66-71] These are particularly interesting systems because they can be directly injected, without the need for implantation, and because they can, in principle, be designed to accumulate at sites of disease by appropriate functionalization of their surface. Thus, rendering these systems electro-responsive can be advantageous for locally releasing entrapped therapeutics using *e.g.*, needle electrodes. When ICPs are used as constituent building blocks for the preparation of polymer nanoparticles, application of an electric potential using two electrodes can be used to release the drug by altering their mutual affinity for one another as described above. The electric field can also drive the migration of charged drug molecules out of an oppositely-charged delivery system. The section presents the most recent work on electro-responsive nanoparticles, micelles, and vesicular structures.

3.1 Nanoparticles

Ge *et al.*[72] have reported drug delivery from electro-responsive PPy nanoparticles dispersed within an injectable temperature-sensitive hydrogel, used to maintain the nanoparticles confined near the injection site (**Figure 7a**). Fluorescein and the chemotherapeutic drug daunorubicin were encapsulated into ~60 nm PPy nanoparticles by emulsion polymerization. An injectable hydrogel was prepared by dispersing the nanoparticles into a solution containing a polymer that induces gelation at 37 ºC. Application of an electric potential between two platinum electrodes led to a more pronounced release of both drugs than diffusion alone. More specifically, when PPy was reduced by the electric potential, its positive charge decreased and caused the release of the negatively-charged fluorescein to keep the overall charge balance. However, upon oxidation, the positive charge of PPy was increased, which led to expulsion of positively-charged daunorubicin (**Figure 7b,c**). The released molecules were further driven by the electric field between the electrodes, which drove the drugs towards the oppositely-charged electrode. This process facilitated escape of the drugs from the hydrogel. No obvious passive release of drugs by diffusion from the PPy nanoparticles within the hydrogel was detected. *In vivo*, electrical stimulation of the injected hydrogel was achieved using two needle electrodes. After each stimulation, the release of

fluorescein was observed by whole animal imaging as an increase of fluorescence (**Figure 7d**). In another example, Ying *et al.*[73] have reported the synthesis of electro-responsive hydrogel nanoparticles for antiepileptic drug delivery by emulsion co-polymerization of 2-dimethylamino ethyl methacrylate, sodium 4-vinylbenzene sulfonate, styrene, acrylate-poly(ethylene glycol)-*N*-hydroxysuccinimidylester (used to graft targeting ligand), and *N,N′*-methylene bisacrylamide (as cross-linker). The surface of the nanoparticles was modified by a brain targeting peptide, angiopep-2. The dispersed nanoparticles increased in size in response to an electrical current (0–500 μA) between two Pt electrodes (separated by 1 cm) immersed into the solution. This led to an accelerated release of the entrapped drug by a factor of ~2 for a current of 200 μA. However, while the antiepileptic activity of the nanoparticles was investigated, analysis of the electro-responsiveness of the nanoparticles *in vivo* was unfortunately not reported.

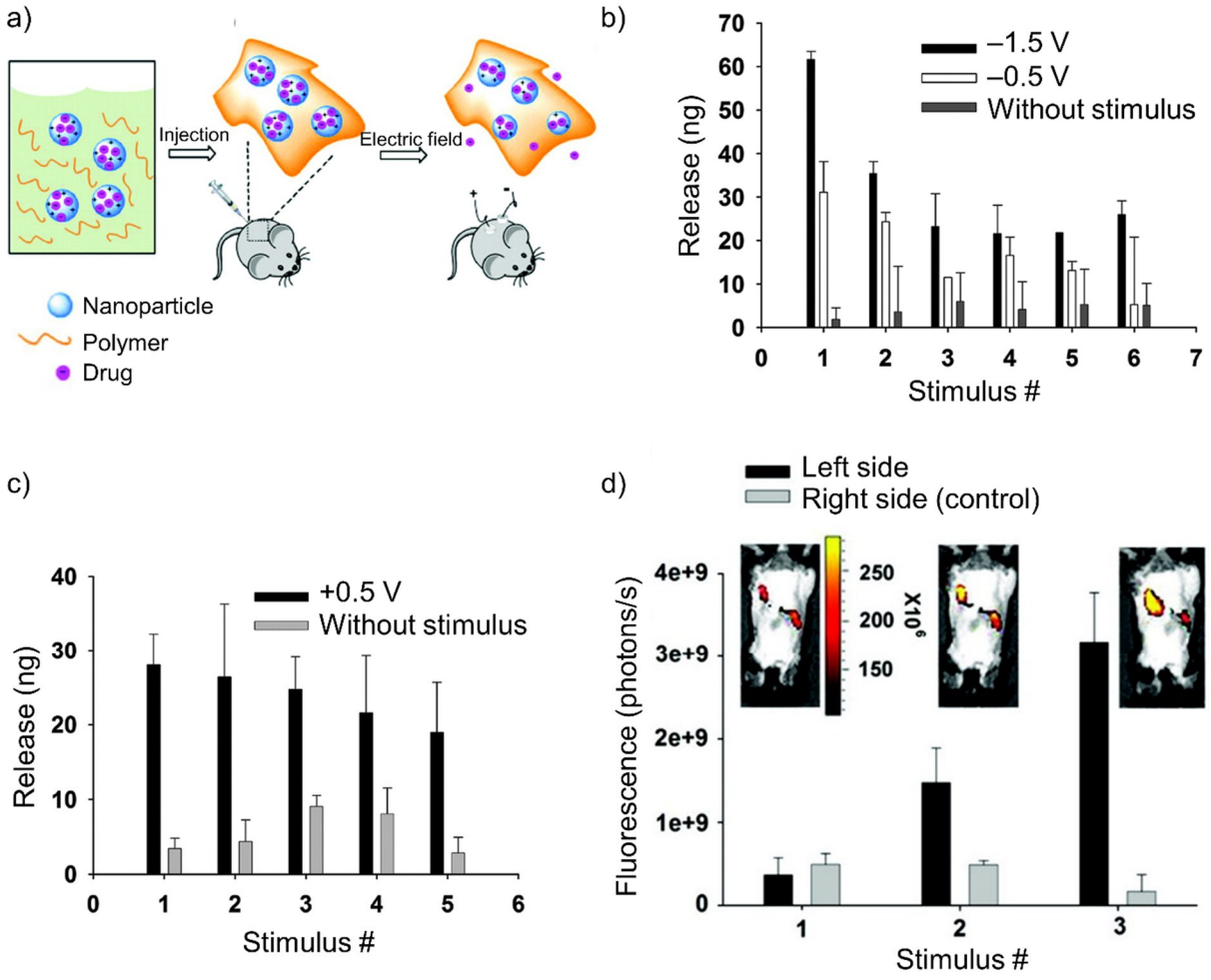

Figure 7| **Drug release from electro-active nanoparticles within a hydrogel matrix.** (a) Electro-active nanoparticles doped with drug can be injected and constrained near the injection site using a thermo-gelling hydrogel. (b) Release of fluorescein by applying a voltage (−0.5 or −1.5 V) between two electrodes for 10 s, repeated every 5 min. (c) Release of daunorubicin by applying a

voltage (+0.5 V) for 10 s, repeated every 5 min. (d) *In vivo* fluorescent images after applying an electric field of −1.5 V·cm^{-1} to the left implanted hydrogel. The right injection site is a control for which no voltage is applied. Adapted with permission from Ge *et al.*[72]

3.2 Polymer Micelles

Micelles are colloidal carriers formed by self-assembly of amphiphilic molecules. Saji *et al.*[74, 75] have developed electro-responsive surfactants that bear terminal ferrocene moieties. In its reduced state ferrocene is hydrophobic, which drives the formation of micelles that can be loaded with hydrophobic drug molecules. Oxidation of ferrocene renders it hydrophilic, which then causes disruption of the micelles. This property was exploited for the solubilisation of water-insoluble compounds, and their subsequent deposition onto electrodes (via electro-destabilization of the micelles). Takeoka *et al.*[76] have built upon this concept and have demonstrated electrochemical control of drug release from redox-active micelles of non-ionic surfactants composed of methoxy poly(ethylene glycol) (mPEG) bearing a terminal ferrocenyl moiety. The micelles disassembled into monomers when they were oxidized, and this process was both reversible and electrochemically-controlled. Release of perylene, used as model drug, was demonstrated upon application of a potential of +0.35 V (vs. SCE) and ON/OFF behavior was observed, suggesting minimal leaching of the drug from the micelles in the absence of a potential, under the conditions examined. The authors suggest that such a strategy could be exploited to locally disrupt micelles at target locations in the body, which could cause the precipitation of hydrophobic drugs at these locations. It would be interesting to pursue the evaluation of the responsiveness of this system in the more complex environment of the body, and in particular upon high dilution and exposure to serum proteins. Dahmane *et al.*[77] have reported the self-assembly of an amphiphilic di-block copolymer composed of mPEG and poly(coumarin methacrylate), which bears electrochemically-responsive coumarin pendant groups. Cyclic voltammetry of the colloidal solution showed diffusion-controlled irreversible oxidation at +1.75 V (vs. SCE), suggesting poor electron transfer between the electrode and the coumarin units buried within the micelles. No spectroscopic changes were observed for coumarin after 15 cyclic voltammetry sweeps, supporting that only a small fraction of micelles (*i.e.*, close to the electrode) were oxidized in each scan. Upon application of a potential of +1.75 V, most of the oxidation of coumarin took place within 54 mins. When subjected to potentials below the oxidation peak, such as 1 V, no electro-activity was observed. Transmission electron microscopy of the solution after electrical disruption of the micelles revealed the presence of aggregates (0.5–1 μm) in coexistence with the remaining micelles. The authors suggest that precipitation could be accounted for by ester bond cleavage between mPEG and poly(coumarin) block. Encapsulation and release of Nile Red from the micelles was evidenced by a shift in the fluorescence spectrum of the fluorophores (expected when it passes to an aqueous environment). More recently, Yuan and co-workers[78, 79] have reported voltage-responsive polymer micelles based on the orthogonal host–guest self-assembly of two polymers via a redox-responsive unit. More specifically, β-cyclodextrin is located on the terminus of one polymer chain, while ferrocene is

located on the second polymer (**Figure 8**). To prepare the amphiphilic di-block copolymer required for self-assembly into micelles, ferrocene must be in its hydrophobic reduced state, so as to enter the hydrophobic cavity of the cyclodextrin. Oxidation of ferrocene to ferrocenium caused it to leave the cyclodextrin, thereby disrupting the co-polymer and thus the micelle. After exposure to an oxidizing potential of +1 V (vs. SCE), micelle disassembly was evidenced by transmission electron microscopy and revealed the precipitation of the hydrophobic block. When these micelles were loaded with the anti-cancer agent paclitaxel, drug release could be achieved over 500 min (at +1 V).

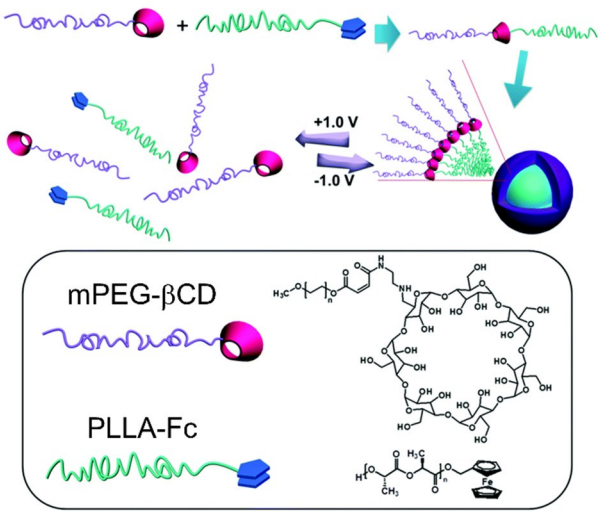

Figure 8| **Drug delivery from electro-responsive micelles**. Voltage-responsive polymer micelles composed of methoxy mPEG and poly(L-lactic acid) (PLLA), connected together via a host–guest interaction between ferrocene (Fc) and β-cyclodextrin (βCD). Oxidation of Fc to ferrocenium leads to polymer and micelle disassembly. Adapted with permission from Peng *et al.*[78]

3.3 Vesicular structures

In addition to forming micelles, the polymers can be designed to self-assemble into vesicular structures termed polymersomes, or even larger entities termed capsules. These systems, in addition to having the ability to load hydrophobic drugs within the hydrophobic domains of their membranes, can also contain an interior aqueous core that can be used to encapsulate hydrophilic drugs. For instance, Kim *et al*. have constructed electro-responsive polymersomes using a rod–coil oligomer composed of tetraaniline and mPEG (**Figure 9**). [80] The oligomer could self-assemble in water into vesicular structures, with tetraaniline sequestering within the hydrophobic membrane. The vesicles collapsed into puck-like micelles by application of oxidative voltage of +0.2 V (vs. Ag/Ag^+), but re-formed using a reductive voltage of –0.5 V, and this transition was fully reversible. This observation was explained by the different packing behavior of tetraaniline within the membrane as a function of its redox status. More specifically, in its reduced form (known as

"leucoemeraldine base") form, a more compact packing is achieved due to the formation of hydrogen bonds between amine and imine. However, upon oxidation to the so-called "emeraldine base" form, a less compact organization is formed, resulting in the supramolecular self-assembly of the system. A dye molecule, fluorescein isothiocyanate, was encapsulated in the vesicles, and full release was observed when the vesicles were oxidized. Tetraaniline units have also formed the basis for the preparation of electro-responsive polymersomes for release of doxorubicin. Wu *et al.*[81] have prepared amphiphilic di-block copolymers composed of thermo-sensitive poly(*N*-isopropylacrylamide) and a tetraaniline segment, which spontaneously self-assembled into vesicles with the ability to respond to temperature, pH, and an electric potential. Application of an oxidizing potential of +0.6 V (vs. Ag/AgCl) resulted in the collapse of the vesicles to form disk-like aggregates. The entrapped chemotherapeutic agent doxorubicin was more rapidly released under an external potential, yet drug leaching from the system was also observed, even in the absence of an external field.

Yoshida *et al.*[82] have reported the preparation of microcapsules composed of physically strong nylon-polystyrene duplicated membranes containing immobilized ferroelectric liquid crystal segments. Microcapsules are larger than polymersomes and their membranes are thicker. When the liquid crystal segment was chiral, a model drug, oxprenolol, encapsulated within the core of the capsule could be released by application of a 2 V potential between two platinum electrodes separated by 3 cm. In contrast, release from microcapsules containing a non-chiral liquid crystal segments was not influenced by an electric field. The authors suggest that the electric field initiated the spontaneous organization of the liquid crystals into a substrate channel from which release of the encapsulated material was easier. However, the precise nature of this channel remains to be determined.

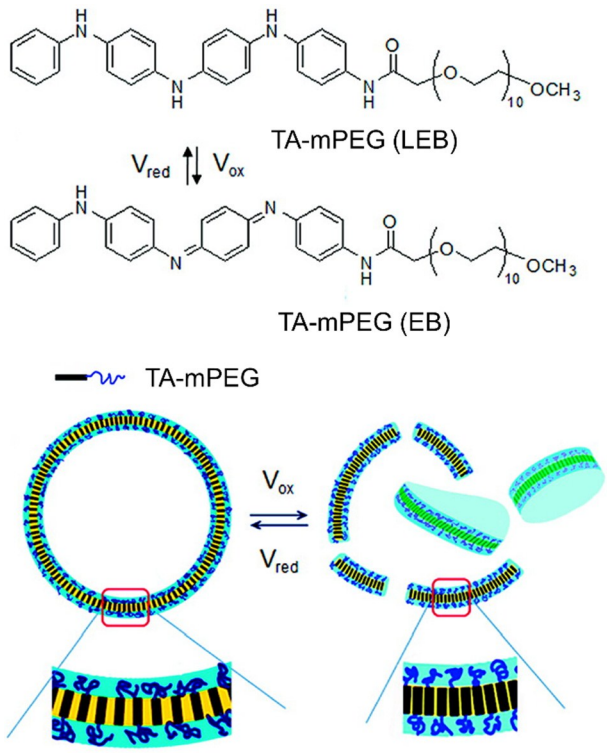

Figure 9| **Drug release from electro-active polymersomes.** Structures of tetra-aniline connected to a short mPEG in its oxidized (TA-mPEG (EB)) and reduced (TA-mPEG (LEB)) states. Self-assembly of TA-mPEG (LEB) yields vesicles, which collapse (reversibly) to puck-like upon oxidation. Adapted with permission from Kim *et al*.[80]

4. Conclusions and outlook

This review has highlighted how nano-engineering is emerging to addressing issues of poor responsiveness and, in certain cases low drug loading, typically associated with bulk ICP delivery systems. It is now an opportune moment for the field to initiate a more in-depth analysis of the biocompatibility of these systems. Furthermore, there is a paucity of data regarding how endogenous biomolecules will interact with these systems and alter their properties. Also, considering their general lack of biodegradability, it is necessary to better assess how, ultimately, they may be eliminated from the body, especially for colloidal/dispersed drug delivery systems that may be difficult to remove surgically. In addition, several studies have shown that reasonably high negative or positive potentials must be applied in order to actuate the system. It will therefore be important to examine the influence of such potentials on sensitive drugs, such as proteins that bear functional groups susceptible to oxidation or reduction, and natural biomolecules in the body that may experience the externally-applied electric potential. Furthermore, very few of the studies mentionned herein have considered the local pH changes produced by the electrochemical oxidation of water reduces the pH locally, or electrochemical reduction of water or dissolved oxygen increases the pH locally, which can also affect the stability of the system.

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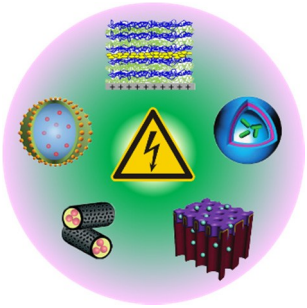
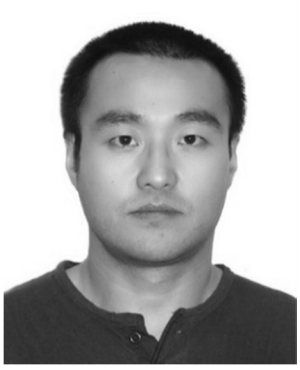
TOC Illustration



Nano-engineering is exploited to address slow drug release and low drug loading of electro-responsive drug delivery systems.

Biographical sketches



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